Remarks

Submission of Exhibits 1-5

Exhibits 1-5 accompany this response. These papers were not earlier presented because Applicant believed the previous response was sufficient to overcome these rejections. Applicant respectfully requests that the declaration and Exhibits be considered.

The Rejection of Claims 27, 28 and 56 Under 35 U.S.C. § 112, First Paragraph

Claims 27, 28 and 56 have been rejected under 35 U.S.C. § 112 first paragraph as not adequately described by the specification. Applicants respectfully traverse the rejection.

Claims 27 and 56 are the independent claims of the rejected claim set. Claim 27 is directed to an *in vitro* method of treating a neoplastic cell. Claim 56 is directed to an *in vitro* method of treating a cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA, or elevated expression of human MDM2 protein. Both methods comprise a step of administering to the cell a therapeutically effective amount of antisense oligonucleotides which are complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene.

To satisfy the written description requirement of 35 U.S.C. § 112, the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d. 1555, 1563-1564 (Fed. Cir. 1991). A specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

In the Office Action dated February 28, 2005, the Patent Office asserted that the claimed methods are not adequately described because the specification fails to provide a sufficient number of representative species of antisense oligonucleotides that will function in the claimed methods. In response to the Patent Office's assertion, applicants indicated the claims are adequately described because the specification provides a coding sequence for human MDM2. One of skill in the art, with the knowledge of a coding sequence of human *MDM2*, would have understood that applicants were in possession of the antisense oligonucleotides employed in the claimed methods because: (1) the coding sequence for human MDM2 provides the nucleotide sequence information needed for one of skill in the art to design and prepare antisense oligonucleotides that inhibit transcription or translation of human *MDM2* and (2) at the time the application was filed, those of skill in the art readily and successfully made and used antisense oligonucleotides that inhibited transcription or translation of a gene based on the gene's sequence. Applicants supported the assertion that one of skill in the art would readily have been able to prepare antisense oligonucleotides able to inhibit transcription or translation of a gene based on the gene's sequence by providing Exhibits A-L. Each of Exhibits A-L was published before the effective filing date of the application and is summarized below:

- Burch *et al.* (Exhibit A) teach that antisense oligonucleotides to the IL-1 receptor gene block its expression in cultured cells *in vitro*.
- Harel-Bellan *et al.* (Exhibit B) teach that antisense oligonucleotides targeted to IL-2 and IL-4 genes inhibit IL-2 and IL-4 gene expression in mouse helper T cell clones.
- Hambor *et al.* (Exhibit C) teach that antisense oligonucleotides targeted the CD8 gene inhibit CD8 gene expression in a human cytotoxic T-cell clone.
- Simons *et al.* (Exhibit D) teach that antisense oligonucleotides targeted to nonmuscle myosin heavy chain (NMMHC) and c-myb genes inhibit NMMHC and c-myb expression in smooth muscle cells (SMCs) *in vitro*.
- Watson *et al.* (Exhibit E) teach that antisense oligonucleotides targeted to c-myc inhibited c-myc expression in MCF-7 cells *in vitro*.
- Sankar *et al.* (Exhibit F) teach that antisense oligonucleotides designed to target

encephalomycarditis virus genes inhibited encephalomyocarditis virus RNA translation *in vitro*.

- Harel-Bellan *et al.* (Exhibit G) teach that an antisense oligonucleotide targeted to c-myc inhibits expression of c-myc protein in human resting peripheral T cells *in vitro*.
- Goodchild *et al.* (Exhibit H) teach that antisense oligonucleotides targeted to HTLV-III nucleotide sequences inhibit HTLV-III gene expression and virus replication *in vitro*.
- Morrison (Exhibit I) teaches that antisense oligonucleotides targeted to bFGF inhibit bFGF expression in a SNB-19 cell line *in vitro*.
- Sumikawa *et al.* (Exhibit J) teach four antisense oligonucleotides targeted to an acetylcholine receptor coding sequence that inhibited transcription or translation of the acetylcholine receptor coding sequence in *Xenopus* oocytes *in vitro*.
- Draper (Exhibit K) teaches that antisense oligonucleotides targeted to HSV inhibit HSV gene expression and replication in an LTK cell line *in vitro*.
- Flood *et al.* (Exhibit L) teaches that antisense oligonucleotides targeted to the *Ly-6A* gene inhibit expression of the Ly-6A protein in LN and D10 cells *in vitro*.

The final Office Action now asserts that Exhibits A-L are not evidence that one of skill in the art would have readily been able to envision, from the nucleotide sequence of a gene, antisense oligonucleotides that would function to inhibit transcription or translation of the gene. The final Office Action cites James (*Antiviral Chemistry and Chemotherapy 2* (1991):191-214) and Branch (*TIBS 23* (1998):45-50) as evidence that antisense oligonucleotides were not readily designed from the sequence of a gene.

The final Office Action cites James as teaching

> Most studies that are published concern one antisense RNA that is inhibitory (frequently covering the entire mRNA; Table 1) and one is aware of a much larger number that do not appear in print which show that an antisense RNA does not inhibit. However, if one confines oneself to a consideration of experiments in which more than one antisense RNA is investigated it is clear that an investigation of the primary structure of an antisense RNA cannot predict whether or not it shall inhibit expression...Since it seems that the primary sequence features of an antisense RNA do not determine whether it is inhibitor[y] it is natural to look at other properties of the molecule such as length, secondary and tertiary structure.

Final Office Action at page 4, lines 4-13, quoting James at page 198, first column.

The Office Action cites Branch as teaching that even years after the filing date of the application the art still recognized obstacles to the use of antisense oligonucleotides in cells. The Office Action cites Branch as teaching,

> Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a target number of candidates for their ability to act inside cells. Monia and co-workers used Northern hybridization to screen 34 20-nt long S-ODNs complementary to *c-raf* kinase and found only one that yielded a greater than fivefold reduction in the target mRNA (Fig. 3a; Ref. 42). Thus, only 3% of the antisense molecules tested in this system were highly effective (Fig. 3b); 40% had almost no effect[42].

Final Office Action at page 4, line 19 to page 5, line 3 quoting Branch at page 49, column 1 bridging column 2. The final Office Action therefore asserts that Exhibits A-L,

> when viewed in light of the James and Branch references provided above, demonstrate that the antisense disclosed to each target gene [in Exhibits A-L], respectively, was determined empirically but not that antisense oligonucleotides complementary to a selected mRNA and that inhibited gene transcription or translation were readily made based on the sequence of the gene.

Final Office Action at page 5, lines 17-21.

Applicants respectfully dispute the conclusion in the final Office Action. The cited teaching in James is evidence that one of skill in the art would, in fact, be readily able to envisage at least one antisense oligonucleotide that would inhibit transcription or translation of a human *MDM2* gene The at least one antisense oligonucleotide is an oligonucleotide complementary to the entire length of human MDM2 mRNA. See James citation above, which teaches, "Most studies that are published concern one antisense RNA that is inhibitory (frequently covering the entire mRNA; Table 1)." Thus, James is evidence that one of skill in

the art would have recognized that applicants were in possession of at least one antisense oligonucleotide that inhibits human MDM2 transcription or translation.

The cited teaching in Branch is evidence that one of skill in the art was able to readily prepare antisense oligonucleotides that inhibit transcription or translation of a gene. Branch, in the description of the Monia reference, teaches that greater than half of the oligonucleotides tested in a screen for antisense activity against *c-raf* inhibited *c-raf* transcription. See Branch at Figure 3B and page 49, column 2, lines 4-7, which teaches that only 40% of oligonucleotides tested displayed no inhibitory activity against transcription of the *c-raf* gene, *i.e.*, 60% of the oligonucleotides tested displayed at least some inhibition of *c-raf* transcription. Thus, Branch's teachings indicate that one of skill in the art would have readily been able to prepare antisense oligonucleotides that inhibited transcription or translation of a gene.

Moreover, Branch, like James, provides evidence that one of skill in the art would have recognized that applicants were in possession of species of antisense oligonucleotides that inhibit human *MDM2* transcription or translation. As discussed above, Branch teaches that 60% of oligonucleotides tested for inhibitory activity to *c-raf* inhibited *c-raf* transcription. If 60% of oligonucleotides tested for inhibitory activity against human *MDM2* inhibit *MDM2* transcription or translation, even if those oligonucleotides are 1000 nucleotides in length each, the disclosure of a human *MDM2* polynucleotide sequence of 2372 nucleotides in length provides 823 representative species of antisense oligonucleotides that would function in the claimed methods (SEQ ID NO:2 discloses a 2372 nucleotide human *MDM2* gene. There are 1373 overlapping polynucleotides of 1000 nucleotides in length within the 2372 polynucleotide sequence. Sixty percent of the 1373 polynucleotides is 823 species of polynucleotide). Branch is evidence that the specification disclosure of a polynucleotide encoding human MDM2 is an adequate

description of a representative number of species of antisense oligonucleotides that inhibit human MDM2 transcription or translation. One of skill in the art would have recognized that applicants were in possession of the antisense oligonucleotides employed in the claimed methods.

James and Branch do not provide sufficient evidence that one of skill in the art, given the sequence of a gene, would not have readily been able to readily produce antisense oligonucleotides capable of inhibiting transcription or translation of the gene. Therefore, James and Branch do not provide evidence that one of skill in the art would have doubted applicants were in possession of the claimed *in vitro* methods employing "antisense oligonucleotides which are complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene." The claims are adequately described.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 27, 28 and 56 Under 35 U.S.C. § 112, First Paragraph

Claims 27, 28 and 56 have been rejected under 35 U.S.C. § 112 first paragraph as not enabled. Applicants respectfully traverse the rejection.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The test is not merely quantitative, because a considerable amount of experimentation is permissible if the experimentation is merely routine or if the specification in question provides a reasonable

amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

To rebut a rejection of lack of enablement, applicant may present rebuttal remarks, supported by suitable proofs, which demonstrate that one skill in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. See Manual of Patent Examining Procedure (M.P.E.P.) § 2164.05, emphasis in original. Suitable proofs include post-filing date evidence that demonstrates that the claimed invention works. M.P.E.P. § 2164.05.

The Patent Office must weigh all the evidence of record, including the specification and any new evidence supplied by applicant and decide whether the claimed invention is enabled. See M.P.E.P. § 2164.05.

The Patent Office asserts that the claims lack enablement because the specification does not sufficiently disclose how to make and use oligonucleotides that will inhibit transcription or translation of a human *MDM2* gene and the art of making antisense oligonucleotides that inhibited gene expression was unpredictable at the time the invention was filed.

Specification disclosures of how to make and use antisense oligonucleotides

The final Office Action asserts that the claims are not enabled because the specification does not provide sufficient disclosure to indicate which antisense oligonucleotides, complementary to a human *MDM2* gene, will inhibit transcription or translation of human *MDM2*. The Office Action asserts, "The specification as filed provides no examples of treatment comprising administering antisense oligonucleotides of the invention and no guidance as to how

to make or use the antisense oligonucleotides of the invention that will function to provide a treatment as claimed." Final Office Action at page 8, lines 16-20.

It is well settled that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Thus, if at the time the application was filed it was well known in the art how to successfully prepare and use antisense oligonucleotides to inhibit transcription or translation of a gene, the specification need not explicitly teach one of skill in the art how make and use the claimed methods employing an antisense oligonucleotide to inhibit transcription or translation of a human *MDM2* gene. Applicants have provided evidence demonstrating that prior to the effective filing date of the application, April 7, 1992, one of skill in the art would have been able to successfully synthesize antisense molecule for a gene of known sequence, *e.g.*, a human *MDM2* gene, and use it to inhibit transcription or translation of the gene. See Exhibits A-L attached to the response to Office Action filed May 31, 2005 and which are summarized above in the discussion of the written description rejection.

The final Office Action asserts that Exhibits A-L do not adequately demonstrate that the claimed methods are enabled because "the claims in the instant Application are drawn to methods of inhibiting the expression of a particular gene, the human MDM2 gene, *in vitro*, in a cell. The claims are not generally to a composition comprising antisense oligonucleotides and the outstanding rejection is not directed to the composition of the antisense oligonucleotides themselves, but to the lack of enablement of a method of inhibiting human MDM2 gene expression in a cell *in vitro*." Final Office Action at page 15, lines 9-14. Applicants respectfully point out that each of the twelve documents provided as Exhibits A-L teaches a method in which cells in culture, *i.e.*, *in vitro*, are

administered an antisense oligonucleotide complementary to a gene. Each of Exhibits A-L teaches that as a result of administering the antisense oligonucleotide, transcription or translation of the gene decreases. See the description of Exhibits A-L, above. The documents provided as Exhibits A-L, therefore, are evidence that one of skill in the art, at the time the application was filed, would have been able to make and use the methods of claims 27, 28, and 56: *in vitro* methods of treating a cell comprising a step of administering antisense oligonucleotides complementary to human *MDM2,* which thereby inhibit transcription or translation of a human *MDM2* gene.

Moreover, to further substantiate applicants' statements in the specification and evidence provided in Exhibits A-L, applicants submit Exhibits 1-4. Exhibits 1-4 are post-filing date evidence that teach *in vitro* methods of treating a neoplastic cell or a cell overexpressing human *MDM2.* Each of Exhibits 1-4 teaches administering a therapeutically effective amount of antisense oligonucleotides complementary to human MDM2 mRNA to the cell, which inhibits transcription or translation of a human *MDM2* gene.[1]

Capoulade *et al.* (*Blood 97* (2001):1043-1049; Exhibit 1) teaches administering an antisense oligonucleotide (5′-GTTGGTATTGCACAT-3′) complementary to human *MDM2* to a cell line, *i.e., in vitro,* that overexpresses human MDM2. Capoulade *et al.* teach administration of MDM2 antisense oligonucleotides to "BL cells containing wild-type p53 and overexpressing MDM2." Page 1044, column 1, lines 14-15. Capoulade *et al.* teach that the antisense oligonucleotides inhibited translation of the human *MDM2* gene. See page 1047, column 1, lines 33-35, which discloses, "In this study, we have shown that an antisense oligodeoxynucleotide, which targets the mdm2 gene and is able to specifically reduce the level of the protein...."

1 To support enablement of a claimed invention, applicants may submit post-filing date evidence that demonstrates that the claimed invention works. M.P.E.P. § 2164.05.

Chen *et al.* (*Proc. Natl. Acad. Sci. USA 95* (1998):195-200; Exhibit 2) teach administering antisense oligonucleotides (5′-GATCACTCCCACCTTCAAGG-3′) complementary to human *MDM2* to neoplastic cells overexpressing human *MDM2 in vitro*. Chen *et al.* teach that the antisense oligonucleotide inhibited MDM2 expression in the cells. "In this report, we describe the identification and characterization of an *MDM2* antisense phosphorothioate oligodeoxynucleotide that inhibits *MDM2* expression in tumor [*e.g.* neoplastic] cells containing *MDM2* gene amplifications." Page 195, column 2, lines 23-26.

Wang *et al.* (*Int. J. Oncol. 15* (1999):653-660; Exhibit 3) teach administration of antisense oligonucleotides (5′-UGACACCTGTTCTCACUCAC-3′) complementary to human *MDM2* to a neoplastic cell *in vitro*. Wang *et al.* teach that administration of the antisense oligonucleotides inhibit *MDM2* expression in the neoplastic cells. "As illustrated in Fig. 2, anti-MDM2 oligo, Oligo AS, specifically inhibits MDM2 expression in SJSA cells [a human osteosarcoma cell line] and p53 and p21 levels elevated accordingly." Page 655, column 2, line 20 to page 656, column 1, line 2.

Miraglia *et al.* (U.S. Patent No. 6,238,921; Exhibit 4) teach that administration of an antisense oligonucleotide (5′-AGCTTCTTTGCACATGTAAA-3′) complementary to human *MDM2* inhibits *MDM2* expression in a neoplastic human lung carcinoma, A549, cell line *in vitro*. See Table 1 (column 16), which teaches the nucleotide sequence of antisense oligonucleotide 16518 as being 5′-AGCTTCTTTGCACATGTAAA-3′ and Table 3 (column 18), which teaches that antisense oligonucleotide 16518 inhibited MDM2 RNA expression by 82-92%, at dosages of 50 to 400 nM.

Exhibits 1-4, even though published many years after the subject application was filed, employ prefiling date technology combined with the teachings of the subject application. The

table below shows that Exhibits 1-4 use the teachings of the specification and the prefiling date state of the art as reflected by Exhibits A-L and Uhlmann, Exhibit 5. Use of after-filing date technology is not apparent any of Exhibits 1-4.

Oligonucleotide Backbone Chemistry		Mode of Delivery of Oligo to Cells	
Pre-filing date art	Exhibits 1-4	Pre-filing date art	Exhibits 1-4
Phosphorothioate; page 1, lines 3-6 of the abstract of Exhibit E.	Exhibit 1: phosphorothioate; page 1044, column 1, lines 48-52.	Electroporation; page 4011, column 1,lines 40-45 of Exhibit C.	Exhibit 1: Electroporation; page 1044, column 2, lines 3-5.
Phosphorothioate; page 1, lines 3-6 of the abstract of Exhibit E.	Exhibit 2: phosphorothioate; page 197, column 1, lines 5-8.	Complexed with lipids; page 1191, column 1, lines 24-35 of Exhibit A.	Exhibit 2: Complexed with lipids (Lipofectin); page 196, column 1, lines 12-15.
Phosphorothioates and 2'O-methyl ribonucleotides, alone and combined; page 558, col. 2, lines 20-23 of Uhlmann (Exhibit 5).	Exhibit 3: mixed backbone; page 654, column 2, lines 51-54.	Complexed with lipids; page 1191, column 1, lines 24-35 of Exhibit A.	Exhibit 3: Complexed with lipids (Lipofectin); page 655, column 1, lines 17-18.
Phosphorothioates and 2'O-methyl ribonucleotides, alone and combined; page 558, col. 2, lines 20-23 of Uhlmann (Exhibit 5).	Exhibit 4: phosphorothioate; column 16, lines 9-12. Also 2'-methoxyethoxy modifications; column 17, lines 24-27.	Complexed with lipids; page 1191, column 1, lines 24-35 of Exhibit A.	Exhibit 4: Complexed with lipids (Lipofectin); column 18, lines 2-4.

At the time the application was filed, *in vitro* methods of making and using antisense oligonucleotides to inhibit transcription or translation of a gene were well known. See prior filed Exhibits A-L. Furthermore, using the technology available at the time the application was filed, those of skill in the art did, indeed, make and use *in vitro* methods of inhibiting human *MDM2* gene transcription or translation by administering antisense oligonucleotides to human *MDM2* as claimed. See Exhibits 1-4.

Unpredictability in the art

The final Office Action also asserts that the claimed methods are not enabled because the state of the art of antisense oligonucleotide therapy was unpredictable at the time the application was filed. The Office Action cites Branch (*TIBS 23* (1998):45-50), James (*Antiviral Chem. and*

Chemo. 2 (1991):191-214), Rojanasakul (A*dv. Drug. Del. Rev. 18* (1996):115-131), and Agrawal (*Mol. Med. Today 6* (2000):72-81) in support of its position.

The Office Action cites James as teaching

> Most studies that are published concern one antisense RNA that is inhibitory (frequently covering the entire mRNA; Table 1) and one is aware of a much larger number that do not appear in print which show that an antisense RNA does not inhibit. However, if one confines oneself to a consideration of experiments in which more than one antisense RNA is investigated it is clear that an investigation of the primary structure of an antisense RNA cannot predict whether or not it shall inhibit expression.

Final Office Action at page 4, lines 4-10 citing James at page 198, column 1.

James, however, also provides evidence that antisense oligonucleotides are routinely produced by those of skill in the art and are employed to inhibit transcription or translation of a gene. James (published in 1991, prior to the effective filing date of the instant application) teaches of many successes of *in vitro* antisense oligonucleotide therapy. See page 193 which teaches of the successful use of antisense oligonucleotides in inhibiting transcription or translation of *IL-2*, *IL-4*, *c-myc*, *c-myb*, *c-mos*, *c-fms*, and genes of Rous sarcoma virus, vesicular stomatitis virus, influenza, Sendai, and human immunodeficiency virus viruses. In fact, James even teaches that "synthetic oligos have proved to be powerful analytical tools for *in vitro* experiment..." Page 193, column 2, last sentence. Thus, James' teaches that those of skill in the art routinely made and used antisense oligonucleotides to successfully inhibit transcription or translation of a gene.

The Office Action cites Branch as teaching, "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a target number of candidates for their ability to act inside cells." Office Action at page 4, lines 19-21. The standard for determining whether the claims are

enabled does not rest on whether the experimentation is empirical. Thus, even if, *arguendo*, effective antisense molecules to a polynucleotide must be found empirically by screening a large number of target candidates, the claims are enabled if the experimentation required to identify those antisense molecules is merely routine, *i.e.*, is not undue. As evidenced by applicants Exhibits A-L, Exhibits 1-5, and James (cited by the Office Action and described above) such experimentation was routine for one of skill in the art at the time the application was filed.

The Office Action cites Rojanaskul as teaching that

> naturally occurring ONs contain phosphodiester backbones that are easily degraded in a biological environment and therefore must be protected or modified to render stability. In addition, because of their large molecular size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting, potential toxicity and affinity of ONs to the target sites pose major challenges to the successful utilization of these compounds.

Office Action at page 10, lines 1-7. Despite these teachings, Rojanaskul also teaches, at Table 1, of twenty-seven references which teach inhibition of a gene's transcription or translation with antisense oligonucleotides. Thus, Rojanaskul also provides ample evidence that those of skill in the art could produce, by routine experimentation, antisense oligonucleotides capable of inhibiting transcription or translation of a gene.

Finally, the Office Action cites Agrawal as teaching, "It is therefore appropriate to study each antisense oligonucleotide in its own context and relevant cell line without generalizing the results for every oligonucleotide." Final Office Action at page 10, lines 13-15, citing Agrawal at page 80, column 1, paragraph 1. Even if, *arguendo*, one of skill in the art must approach the design of an antisense oligonucleotide to each gene *de novo*, it is apparent that doing so is a routine practice in the art. In fact, Agrawal teaches, "There are numerous examples in which PS-oligonucleotides of varying lengths and base compositions have been employed to inhibit the

translation of cellular or foreign gene by an antisense mechanism." Page 73, column 1, lines 8-11.

Applicants provided comments pointing out teachings in the Rojanaskul and Agrawal references which indicate that the claimed methods are enabled in the response to Office Action dated May 31, 2005. However, the final Office Action asserts that these comments were not persuasive "because the claims in the instant Application are drawn to methods of inhibit the expression of a particular gene, the human MDM2 gene, *in vitro*, in a cell. The claims are not drawn generally to a composition comprising antisense oligonucleotides and the outstanding rejection is not directed to the composition of the antisense oligonucleotides themselves, but to the lack of enablement of a method of inhibiting human MDM2 gene expression in a cell *in vitro*." Final Office Action at page 13, line 20 to page 14, line 3. Applicants respectfully point out that the teachings in James, Rojanaskul, and Agrawal all demonstrate that administering an antisense oligonucleotide complementary to a gene in an *in vitro* method results in inhibition of transcription or translation of the gene. Therefore, the teachings cited by applicants in these references are pertinent to the claimed *in vitro* methods.

The Weight of the Evidence

The Patent Office has cited four references, Branch, James, Rojanaskul, and Agrawal as evidence that at the time the application was filed the art of employing antisense oligonucleotides to inhibit the transcription or translation of a gene, *e.g.*, a human *MDM2* gene, was unpredictable. The Patent Office has also cited the lack of teachings in the specification to assert that the claims are not enabled.

Applicants have cited twelve documents, Exhibits A-L, as evidence that prior to the effective filing date of the application one of skill in the art was able to make and use an

antisense oligonucleotide to a gene that was able to inhibit the gene's transcription or translation *in vitro*. Applicants have also provided four documents, Exhibits 1-4, as evidence that after the filing date of the application those of skill in the art did, in fact, make and use antisense oligonucleotides to a human *MDM2* gene that inhibited the transcription or translation of *MDM2 in vitro*. Applicants have further cited evidence in the Patent Office's four references which substantiates applicants' assertions that antisense oligonucleotides that inhibited transcription or translation of a gene *in vitro* were routinely successfully produced by those of skill in the art.

The weight of the evidence favors enablement of the claims. Applicants respectfully request withdrawal of this rejection.

Respectfully submitted,

Dated: November 22, 2005

By: 
Michelle Holmes-Son
Registration No. 47,660

Banner & Witcoff, Ltd.
Customer No. 22907